the need for insulin zinc suspension (amorphous). It is suggested that this would be possible if the properties of the acetate buffer in insulin zinc suspension were altered, but that further studies are required.

The indications for the use of the insulin zinc suspensions are described, and a plan is outlined for changing patients to the new preparations.

We wish to thank the Novo Laboratories in Copenhagen and Evans Medical Supplies Limited, their distributors in this country, for very generous supplies of these insulins for use in this trial. We would also like to thank Miss A. Moxham, who performed most of the blood-sugar estimations, and the dietitians, sisters, and nurses for the great help they have given us.

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# THE CLASSIFICATION OF VARIOUS INSULINS

BY

**F. GERRITZEN, M.D.**

*(From the Department of Endocrinology and Diseases of Metabolism, University Hospital Medical Department, Leyden, Holland)*

In an annotation in the *British Medical Journal* (1953) in which the Novo insulin preparations were announced, attention was drawn to the confusion that might arise when a larger variety of insulins became available. This problem needs extensive consideration for several reasons.

In some cases the new insulin preparations show no superiority over those already in use, but in others they are a distinct improvement. Most doctors who treat diabetic patients use a special brand of insulin, and thus do not take advantage of the intensive research that is going on in the laboratories of the insulin manufacturers.

To choose the right insulin for a certain diabetic patient is not a simple matter. It requires a thorough study of the particular manifestations of the case and a knowledge of the characteristics of the various insulins existing, to adapt the insulin therapy to the individual need. It would be of great value, therefore, if the physician could be guided in the choice of the most suitable insulin, or, if the patient is already using insulin, in making a change that might be of benefit in the particular case.

## Principles Involved in Choosing Type of Insulin

In this study a method is recommended which has been described earlier (Gerritzen, 1952), but it might be useful to recall attention to the principles that led to its adoption. Though insulin is used almost exclusively in diabetics, no reliable information can be had from an investigation of diabetic patients because they vary widely in sensitiveness to it. The results obtained would tell us more about the variation in sensitiveness of the patients than about the insulin itself. The same consideration would apply if, in the standardization of insulin, diabetic instead of healthy rabbits were used. The results would be far more uncertain if diabetic rabbits with different degrees of the metabolic disorder served as test animals. Evidently the diabetic patient would not be a suitable subject for testing the properties of different insulins. Even the average of several diabetics, if an average could be calculated, would not be better, as the average diabetic does not exist.

Insulin is measured in terms of the decrease of the blood sugar after injection. This means that if the decrease in the blood sugar is representative of the action of insulin, all other factors influencing the blood sugar must be excluded. Fasting and exercise, which tend to depress the blood sugar, must be avoided; in addition, emotions and meals, which cause an increase of blood sugar, should also be excluded. Elimination of exercise is easy in the human, as the test persons can be kept in bed. The requirements to exclude meals and to avoid a fasting state led me to give a constant amount of carbohydrate every hour, a method that is not practicable in test animals, because the emotion of forced feeding would undoubtedly influence the blood sugar. Test animals in a state of fasting would get low blood-sugar values when insulin was injected, and a regulating mechanism, of which adrenaline is the most important component, might come into action, thus making the results of insulin action very uncertain.

For these reasons I choose healthy students as test persons. The results obtained in regard to duration and character of the action of insulin would not, of course, apply to diabetics, but they would tell us something about the qualities of the various insulins. This has become of special importance since Hallas-Møller *et al.* (1952a, 1952b) published their method of testing insulin in diabetics. In a great number of diabetics they classified the reaction to different insulins as types A, B, and C; type B being the ideal one, as it gives a flat blood-sugar curve throughout the day. It is necessary to give the A-type (⌣) patient an insulin that has a more prolonged action with less intensity during the first few hours after injection, while patients of type C (⌢) require an insulin of shorter and more intense action.

This logical attempt to adjust the insulin to the type of reaction of the patient presupposes a knowledge of the differences that exist between the various insulins. This study is an effort to classify the insulins in regard to the duration and character of the action.

The persons tested were lying down from 11 p.m. the night before the experiment started and during the experiment. From 6 a.m. on the day of the experiment they ate 50 g. of mashed potatoes (about 10 g. of carbohydrate) and drank 30 ml. of water every hour. From 7 a.m. the blood sugar was determined hourly by the Hagedorn–Jensen method, until the end of the experiment, which was considered to be reached when the average blood sugar had returned to its original level at 8 a.m.

By this method I was able to classify 13 different insulins without difficulty into four categories according to the duration of the action. Differences in the intensity of the action, as measured by the depression of the blood-sugar level, are shown in Figs. 1–4. The insulin mixtures are described in my previous study (Gerritzen, 1952), but are not considered here.

In an earlier investigation (not published) I found that the sensitivity of healthy students to insulin does not vary throughout the day. Therefore the fact that the prolonged insulins act throughout the evening and night does not affect the results.

## Duration of Action

*Category 1.* — Duration, eight hours. Only two insulins were tested—regular

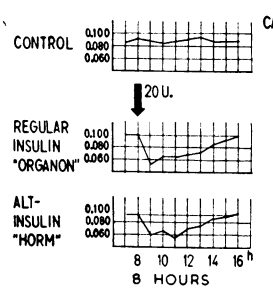


FIG. 1.—Category 1. Duration of action, 8 hours. Both insulins act during the same period of time. Regular insulin (Organon) reaches its maximum in one hour. Alt-insulin (Horm) acts less acutely.

insulin (Organon) and alt-insulin (Horm)—the former acting somewhat more acutely than the latter. In the literature the normal duration of the action of regular insulin in diabetics is given as eight hours, so one may take this value to be well founded (Fig. 1).

*Category 2.*—Duration, 10 hours. To this category belong N.P.H. insulin (Organon), N.P.H. 50 (Lilly), depot insulin (Horm), semilente (Novo), and zinc insulin "neutrale" (Organon). These show only minor differences in character. The first three insulins are protamine zinc insulins: N.P.H. insulin and N.P.H. 50 being cloudy suspensions and depot insulin (Horm) a clear solution. The last two insulins are zinc insulins, consisting of zinc and insulin only (Fig. 2).

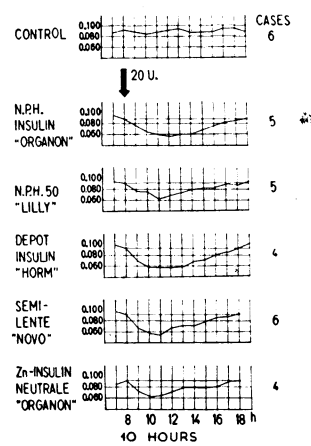


FIG. 2.—Category 2. Duration of action, 10 hours. These five insulins have a nearly identical action—only minor variations in intensity.

*Category 3.*—Duration, 16 hours. Di- and iso-insulin, globin insulin, and lente (Novo) belong to this group. Di- and iso-insulin are chemically modified insulins with prolonged action. Globin insulin has a prolonged action due to the addition of oxyhaemoglobin, while lente is a zinc insulin, a mixture of semilente and ultralente (Fig. 3).

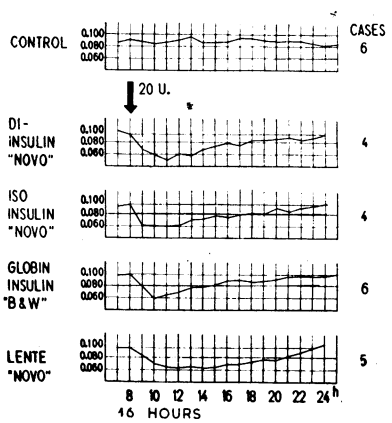


FIG. 3.—Category 3. Duration of action, 16 hours. Of the insulins of this class, lente has the smoothest action.

*Category 4.*—Duration, 18 hours. Protamine zinc insulin and ultralente are at present the insulins with the most prolonged action. According to Hagedorn, P.Z.I. acts about twice as long as regular insulin, a statement that is in agreement with the findings presented here: regular insulin, 8 hours; P.Z.I., 18 hours (Fig. 4).

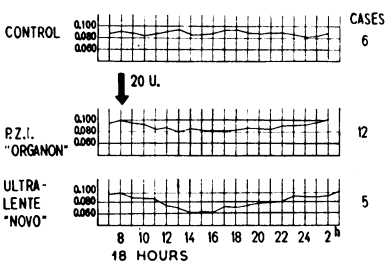


FIG. 4.—Category 4. Duration of action, 18 hours. These insulins have the most prolonged action of all the insulins at present on the market.

I wish once again to point out that the recorded durations do not mean that a certain insulin will act during that time in an individual diabetic patient. For some reason or other insulin may act for a much longer period of time when injected in diabetic patients (Figs. 3 and 4). This is a question of individual sensitivity more than an indication of the character of the insulin. Hallas-Møller's method of arriving at the most suitable insulin seems logical, but a knowledge of the differences existing between the various insulins, measured under standard experimental conditions in an identical test material, is a prerequisite for its practical application.

The description of these insulins, which comprise only a few of those on the market, leads to the question whether one preparation is preferable to another of the same category. This question I have not tried to answer.

## Summary

Thirteen different insulins have been tested in young healthy students under standard experimental conditions—that is, absolute rest and a constant hourly intake of carbohydrate and water.

These insulins have been classified into four categories, according to the duration of the action, with the object of simplifying the choice of the most suitable insulin.

I have to thank Miss S. P. I. Hoogeveen for accurate and numerous blood-sugar determinations, and the managements of Burroughs Wellcome, Hormonchemie, Novo, and Organon for financial support.

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# Medical Memoranda

## An Early Fatal Reaction to Blood Transfusion

Fatal haemolytic transfusion reactions due to specific incompatibility between the blood of the donor and recipient are fortunately rare. The fatal haemolytic reaction here recorded was the result of confusing the recipient's name with that of the donor's label, both donor and recipient having the same surname. The duration of the reaction, which was four hours, must be regarded as one of the shortest on record.

### CASE REPORT

After an abdomino-perineal excision of the rectum for carcinoma on February 10, 1953, a man aged 54 received 2 pints (1,140 ml.) of blood of his own group, O rhesus-positive, followed by intravenous dextrose-saline. In the early hours of February 11, on account of bleeding from the perineal wound, the night sister, thinking that the patient required more blood and acting on unreliable information that the blood had been prepared and would be available in the pathological laboratory, went to the blood bank about 3.30 a.m. and, on finding a bottle with a donor's label bearing the name Moon (which was the patient's name), took it to the ward and began the transfusion. The blood was group B rhesus-positive, and did not bear a compatibility label. It ran very slowly from 4 to 5 a.m., when it stopped. The resident doctor, after relieving the blockage in the needle, allowed the blood to flow rapidly from 6 to 6.20 a.m., when the patient had a severe rigor lasting 10 minutes. He had pyrexia and a rapid pulse, and seemed distressed. For the next three and a half hours, until his death at 10 a.m., he had suffered from severe shock, with pyrexia, rapid pulse, increased respirations, and epigastric pain. He had survived four hours after receiving a rapid transfusion of about 300 ml. of incompatible blood.

*Post-mortem Examination.*—This was conducted about two hours after death and revealed little retroperitoneal haemorrhage. The blood serum was very haemolysed. When anti-B serum was mixed with the patient's cells there was no agglutination, indicating that complete, or almost complete, destruction of all the transfused cells had taken place. A comparison of pre- and post-transfusion titres to anti-A and anti-B in the patient's serum was made. (1) The titre of anti-A was 1:8 in both pre- and post-transfusion